REMARKS

Claims 1-34 and 36-73 are pending. Claims 1-34, directed to methods of treating hepatitis virus infections, have been cancelled, and will be pursued in a copending application, U.S. Ser. No. 09/355,446, which is discussed below. Claims 37-41, 43-46, 53-56, 58, 61, 65, 66, 70 and 71 have been amended, as discussed below. Support for the amendments to the claims may be found, for example, at pages 12-14 of the specification.

The title of the application has been amended to reflect the cancellation of the method claims.

Copending application

In compliance with MPEP 2001.06(b), Applicants advise the Examiner of the copendency of U.S. Ser. No. 09/355,446 (Atty. Docket No. PHA 6180), which originally contained claims identical to those under prosecution in the instant application.

An IDS filed in the instant application on August 11, 2000, submits prior art that is referred to as having been cited in another copending application, i.e., U.S. Ser. No. 09/249,220 (Atty. Docket No. PHA 6109). Both the instant application and Ser. No. 09/355,446 have also been made of record in Ser. No. 09/249,220. Applicants' undersigned attorney had intended to also make of record the relationship between the instant application and both the '220 and the '446 application; and has been proceeding on the belief that this had long ago been done. However, a review of the files after receipt of the most recent notice of allowance in the '446 application has revealed that no record had been made of this case in '446, or in '446 of this case. Nor has any record been made of the relationship between the claims of the instant case and the claims of '220.

The '220 application contains claims that overlap the claims of the instant application and may substantially dominate the instant claims as currently amended. The '220 application was rejected in an Office action of November 22, 2000. Applicants filed a response on April 23, 2001. On September 13, 2001, the PTO issued a restriction requirement, which Applicants responded to on October 15, 2001. No further action has been received from the PTO. A status inquiry was submitted June 12, 2002.

Applicants also advise that claims identically corresponding to those of the instant application had been allowed in Ser. No. '446 on June 26, 2002, after consideration of all art of record herein. A Request for Continued Examination was filed in that case on September 26, 2002, cancelling the pharmaceutical composition claims and advising the Examiner in that case of the copendency of the instant application. The instant amendment cancels method claims 1-34 from the instant application. These claims had been previously allowed, and will continue to be pursued, in Ser. No. '446.

The '446 application is under examination by Examiner James Wilson (308-4624), and the '220 application by Examiner Jeffrey Fredman (308-6568). Upon request by the Examiner herein, Applicant will supply prosecution papers from the '446 and '220 files.

Objection to the specification and claims 1-19, 22-31, 36-54 and 58-66 under § 112, first paragraph

Reconsideration is requested of the rejection of the specification and claims 1-19, 22-31, 36-54 and 58-66 under § 112, first paragraph, for lack of enablement.

Applicants respectfully disagree with the Office's assertion that the specification does not satisfy the requirements of

§ 112, first paragraph. The definition of the phrase "antiviral compound" is well-recognized in the art, and the phrase does not require further definition or criteria. For example, attached is an excerpt from Dorland's Medical Dictionary, which defines "antiviral" as:

> 1. destroying viruses or suppressing their replication. 2. an agent that destroys viruses or suppresses their replication.

As those skilled in the art understand, antiviral nucleosides and nucleotides function at least to suppress replication of viruses, if not to destroy them. The exact mechanism by which the suppression occurs may vary depending on the identity of the nucleoside or nucleotide and the virus against which it is administered, but generally these compounds are known to be effective in suppressing replication at one or more stages in the attack of a virus upon a host cell or use by the virus of cell biochemistry for its reproduction.

Whether a particular compound has activity against a particular virus, in this case hepatitis virus, is readily determined by one skilled in the art. Numerous *in vitro* antiviral assays wherein the efficacy of a particular compound in inhibiting one or more hepatitis viruses or virus strains are available. The specification provides an example of such an assay, see Example 3, and others are known in the art as of the filing date of the instant application. These assays are readily available and routinely used. Similarly, *in vivo* antiviral assays such as the woodchuck animal model known in the art and described in Examples 4 and 5, and other animal models known to those skilled in the art (e.g., Peking duck and California ground squirrel models), are available. See, e.g., Tennant et al., "Animal Models in the Preclinical Assessment of Therapy for Viral Hepatitis," College of Veterinary Medicine, Cornell University,

Ithaca, NY *Antiviral Therapy* (1996), 1 (Suppl. 4, Therapies for Viral Hepatitis), 47-52, an abstract of which is attached hereto. By using of one or more of these assays, a skilled artisan can readily determine whether particular nucleosides, nucleotides, or mixtures thereof described in the specification, are antiviral compounds.

The specification lists over thirty nucleosides and nucleotides by name, and describes in detail the class of nucleoside and nucleotide compounds. Indeed, the Office has acknowledged that "[b]ased on the instant disclosure, the skilled artisan would have no problem identifying those compounds falling into the classes of nucleotide[s], or nucleosides envisioned by Applicants." See Paper no. 10, page 7.

While the pharmaceutical art may be somewhat unpredictable, assays available to determine whether a particular compound is an antiviral compound are routinely performed by skilled artisans. The mere fact that some experimentation may be necessary to select antiviral compounds not named in the specification does not render the specification non-enabling:

> 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' MPEP 2164.06, citing In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

The *in vitro* assays described in the specification and known to those skilled in the art are routine assays. The specification does describe antiviral nucleoside and nucleotide compounds that are useful in the invention, as the Office has acknowledged, and over thirty of these compounds are identified by name. One skilled in the art could perform the routine assays described in

the specification to determine other antiviral nucleosides and nucleotides useful in the invention without undue experimentation.

For the above reasons, Applicants assert that the specification satisfies the requirements of § 112, first paragraph.

Claims 1-19, 22-31, and 36 have been cancelled, thereby rendering moot the objection to these claims under § 112, first paragraph.

Claims 37-54 and 58-66, for the same reasons given above with respect to the specification, also satisfy the requirements of § 112, first paragraph.

Rejection of claims 1-19, 22-31, 36-54 and 58-66 under § 112, second paragraph

Claims 1-19, 22-31, and 36 have been cancelled, thereby rendering moot the rejection of these claims under § 112, second paragraph.

Reconsideration is requested of the rejection of amended claims 37-54 and 58-66 under § 112, second paragraph, as indefinite.

The Office asserts that claims 37-54 and 58-66 fail to clearly set forth the metes and bounds of the patent protection desired due to reference to "antiviral compounds," and that the specification does not provide criteria that define medicaments that "fall under the 'antiviral compound' penumbra." As discussed above, however, the definition of the phrase "antiviral compound" is well-recognized in the art, and the phrase does not require further definition or criteria. Whether a particular compound has activity against a particular virus, in this case

hepatitis virus, is readily determined by one skilled in the art, who can make use of any number of *in vitro* or *in vivo* assays available in the art, and known to skilled artisans, at the time the instant application was filed.

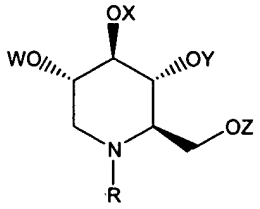
MPEP 2173.02 requires that definiteness of a claim be analyzed in light of the disclosure of the instant application, the teachings of the prior art and the claim interpretation that would be given by one of ordinary skill in the art at the time the invention was made. Analyzed in this light, the phrase "antiviral compound" does not render claims 37-54 and 58-66 indefinite, and these claims satisfy the requirements of § 112, second paragraph.

Rejection of claims 36-40, 43-45 and 48-51 under § 102

Claim 36 has been cancelled, rendering moot its rejection under § 102(a) and (b).

Reconsideration is requested of the rejection of amended claims 37-40, 43-45, and 48-51 under § 102(b) as anticipated by Westarp et al., German Patent No. DE 43 07 883 A1, and under § 102(a) as anticipated by Chang et al., U.S. Patent No. 5,750,648.

As amended, claims 37-40, 43-45 and 48-51 depend directly or indirectly from claim 70. Claim 70, as amended, is directed to a pharmaceutical composition comprising a first amount of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I, a second amount of an antiviral compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and mixtures thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. The compound of Formula I has the following structure:



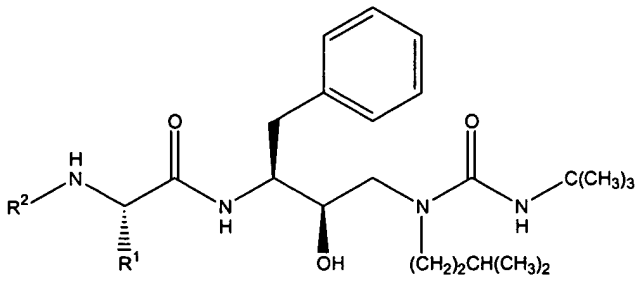
I

wherein R is selected from the group consisting of arylalkyl, cycloalkylalkyl, and branched or straight chain alkyl having seven or more carbon atoms, and W, X, Y, and Z are as defined in the claim. 1,5-dideoxy-1,5-imino-D-glucitol compounds are also known as DNJ compounds.

Claim 37, as amended, defines R in the same manner as claim 70 (i.e., R is selected from the group consisting of arylalkyl, cycloalkylalkyl, and branched or straight chain alkyl having seven or more carbon atoms). Claims 38, 43, and 48-51, as amended, define R as a branched or straight chain alkyl having seven or more carbon atoms. As amended, claims 39 and 44 define R as a straight chain alkyl having a chain length of C_7 to C_{20}, and claims 40 and 45 define R as a straight chain alkyl having a chain length of C_7 to C_{14}.

Westarp et al. describe treatment of motor neuronal disorders such as ALS by administration of anti-retroviral compounds (e.g., anti-HIV compounds) alone or in combination with one another. Among the numerous classes of compounds disclosed are nucleoside and nucleotide analogues (e.g., AZT and ddI), and the iminosugars DNJ and N-butyl-DNJ. Others include reverse transcriptase inhibitors, isoquinoline protease inhibitors, phosphonoacetic acid analogs, and antidepressants.

Chang et al. describe novel HIV-protease inhibitors and their use in the treatment of HIV infection. The protease inhibitors have the following structure:



wherein R^1 and R^2 are as defined in the reference. In addition, Chang et al. describe the use of these protease inhibitors in combination, either as separate compositions or as a single composition, with one or more anti-HIV compounds including nucleoside and non-nucleoside retroviral reverse transcriptase inhibitors, other HIV-protease inhibitors, and glucosidase inhibitors including N-butyl-DNJ and its per-butyl ester.

As amended, none of claims 37-40, 43-45, and 48-51 are anticipated by Westarp et al. or Chang et al. The only N-substituted DNJ compound described by Westarp et al. is N-butyl DNJ; Chang et al. mention only N-butyl DNJ and its per-butyl ester. None of claims 37-40, 43-45 or 48-51 define R to include butyl, and thus claims 37-40, 43-45, and 48-51 are novel in view of Westarp et al. and Chang et al.

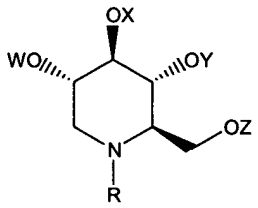
Rejection of claims 1-34 and 36-73 under § 103

Claims 1-34 and 36 have been cancelled, rendering moot the rejection of these claims under § 103.

Reconsideration is requested of the rejection of amended claims 37-73 under § 103 as unpatentable over Block et al., Proc. Nat'l. Acad. Sci. USA (1994) 91:2235-2239 ("Block I") and U.S. patent No. 6,037,351 ("Block II"); Repp et al., J. Biol. Chem. (1985) 260:15873-15879; Applicants' admissions on the record; and Gish et al., Exp. Opin. Invest. Drugs (1995) 4:95-115.

Claims 37-69, as amended, depend directly or indirectly from claim 70. Claim 55 has been amended to delete a compound outside the scope of claim 70 (i.e., N-(n-hexyl-)-1,5-dideoxy-1,5-imino-D-glucitol, see line 5 of claim 55) and to correct an obvious typographical error (i.e., replacing N-(1-pentylpentylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol and N-(1-pentylpentylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate, see lines 24 and 55-56 of claim 55, with N-(1-pentylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol and N-(1-pentylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate, respectively).

Claims 70-73 are independent claims. Claim 70, as amended, is directed to a pharmaceutical composition comprising a first amount of an N-substituted-DNJ compound of Formula I, a second amount of an antiviral compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and mixtures thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. The compound of Formula I has the following structure:



I

wherein R is selected from the group consisting of arylalkyl, cycloalkylalkyl, and branched or straight chain alkyl having seven or more carbon atoms, and W, X, Y, and Z are as defined in the claim.

Claim 71, as amended, is directed to a pharmaceutical composition comprising a first amount of an N-substituted-DNJ compound of Formula I, a second amount of an antiviral compound, and a pharmaceutically acceptable carrier, diluent, or excipient. The structure of Formula I is as shown above for claim 70, and R is selected from the group consisting of arylalkyl,

cycloalkylalkyl, and branched or straight chain alkyl having a chain length of between C_7 and C_{20}, and W, X, Y, and Z are as defined in the claim. The antiviral compound is selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and mixtures thereof.

Claim 72 is directed to a pharmaceutical composition comprising a first amount of an N-substituted-DNJ compound of Formula I (defined as in claim 70), a second amount of (-)-2'-deoxy-3'-thiocytidine-5'-triphosphate (3TC), and a pharmaceutically acceptable carrier, diluent, or excipient.

Claim 73 is directed to a pharmaceutical composition comprising a first amount of an N-substituted-DNJ compound of Formula I (defined as in claim 70), a second amount of an antiviral compound selected from a group consisting of thirty-five specific compounds, and a pharmaceutically acceptable carrier, diluent, or excipient.

Block I discloses that secretion into the culture media of human Hepatitis B virus (HBV) is inhibited by N-butyl-DNJ.

Block II discloses a method of inhibiting HBV using N-alkyl-DNJ compounds in which the N-alkyl group contains from three to six carbon atoms. As background, Block II mentions the use of a nucleoside analog, fialuridine, for treatment of chronic hepatitis B, but reports that clinical tests of this compound have been suspended due to drug-related liver failure in six of the twenty patients studied. See col. 1, lines 41-44. Similar results are reported in the specification of the instant application, see page 4, lines 16-20.

Repp et al. disclose inhibition of mouse hepatitis virus (MHV) by glucosidase inhibitors such as DNJ and N-methyl-DNJ.

Gish et al. disclose a number of agents for the treatment of chronic HBV infection, including immune modulating agents, vaccines, herbal therapy, nucleoside analogues, synthetic oligodeoxyribonucleotides, antisense molecules and decoys. They present a general discussion of the potential benefits of combination therapies, and remark that "the future use of immunomodulating agents such as interferon or interleukin with a nucleoside analogue appears promising." See page 107. Nowhere do Gish et al. so much as mention DNJ or its N-substituted derivatives, either alone or in combination with any anti-hepatitis agent.

As acknowledged by Applicants and as stated in the specification, DNJ and its N-alkyl derivatives are known inhibitors of the N-linked oligosaccharide processing enzymes alpha glucosidase I and II, see page 2, lines 30-35, and have potential to inhibit glucose transport, glucosyl-transferases, and/or glycolipid synthesis, see page 2, line 35 through page 3, line 5. Applicants have further acknowledged that N-alkyl-DNJ compounds wherein the alkyl group has from three to six carbons have been shown to be effective in the treatment of hepatitis B infection, see page 3, lines 11-20.

The Office has failed to establish that claims 37-73 are *prima facie* obvious over the prior art. The Office asserts that it is "*prima facie* obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose." (The Office further states that "the instant claims define . . . the concomitant use of two conventional anti-inflammatory agents." Presumably, use of the term "anti-inflammatory" was unintentional.) However, Block I, Block II, Repp et al., and Gish et al. neither disclose nor suggest that the N-substituted DNJ compounds within the scope of amended claims 37-73 are active against hepatitis virus. Nor have

Applicants admitted that these N-substituted DNJ compounds were known in the art as hepatitis inhibitors. In fact, these compounds are not known to be hepatitis inhibitors, at least so far as the present record shows or Applicants are aware. Applicants have acknowledged that N-alkyl DNJ derivatives are known inhibitors of the N-linked oligosaccharide processing enzymes alpha glucosidase I and II, see page 2, lines 30-35, and that as glucose analogs, they have potential to inhibit glucose transport, glucosyl-transferases, and/or glycolipid synthesis, see page 2, line 35 through page 3, line 5. Applicants have not, however, acknowledged that the N-substituted DNJ compounds described in claims 37-73 were known in the art as anti-hepatitis compounds.

The only N-substituted-DNJ compounds disclosed as active against hepatitis in the cited references are N-butyl-DNJ (Block I and Block II); N-alkyl-DNJ compounds having from three to six carbons in the N-alkyl group (Block II and the instant specification, see page 3, lines 11-20); and N-methyl-DNJ (Repp et al.). As noted above, Gish et al. do not disclose any N-substituted-DNJ compounds. And, none of the references cited by the Office suggest selecting the N-substituted-DNJ compounds described in claims 37-73. Applicants have selected N-substituted DNJ compounds not previously disclosed as having anti-hepatitis virus activity and have combined them with nucleoside and/or nucleotide antiviral compounds to prepare the compositions of the instant claims.

To establish that a claim is *prima facie* obvious in view of the prior art, the Office must show that the prior art reference(s) teach or suggest all the claim limitations, and that there is a motivation in the art to combine the references with a reasonable expectation of success. With regard to amended claims 37-73, the Office has not met even the first hurdle, i.e., the PTO has not shown that the N-substituted-DNJ compounds of claims

37-73 are taught or suggested by any of Block I, Block II, Repp et al., Gish et al., or Applicants' admissions on the record, taken alone or together. The Office has not because it cannot.

Furthermore, the actual teachings of Block I, Block II, Repp et al., and Gish et al. particularly fail to make it obvious to select the N-substituted-DNJ compounds and the nucleoside or nucleotide antiviral compounds of claims 37-73, out of the many agents that individually show activity against HBV (see, e.g., Gish et al.) and to combine these compounds in compositions. Among the many compositions proposed in the art for treatment of hepatitis infections, the cited references offer no guidance which would have enabled one skilled in the art to select the N-substituted-DNJ compounds described in claims 37-73 for combination with nucleoside or nucleotide antiviral compounds in general, as in claims 37-54, 58-66, 70 and 71, or with the particular antiviral compounds of claims 55-57, 67-69, 72 and 73.

Obviousness must be assessed against the entire background of the art, see In re Kuderna, 165 U.S.P.Q. 575, 578-79 (CCPA 1970). If anything, Block II tends to distance N-substituted-DNJ compounds from nucleosides, inasmuch as it teaches therapy with certain N-alkyl-DNJ compounds alone, while recounting unfavorable experiences with an example of the latter:

> Clinical tests on the use of the nucleoside analog, fialuridine, for treatment of chronic hepatitis B were suspended recently due to drug-related liver failure in six of 20 patients. Consequently, there is a great need for a safe drug treatment of hepatitis B.

See Block II, col. 1, lines 41-44.

Applicants, on the other hand, selected N-substituted-DNJ compounds not disclosed in the cited art for treatment of

hepatitis infections; selected nucleoside or nucleotide antiviral compounds from the many antiviral compounds known in the art; chose further to administer the N-substituted DNJ compounds in combination with nucleosides, nucleotides, or mixtures thereof; formulated a composition comprising the same; and have demonstrated the efficacy of the combination therapy for inhibiting hepatitis virus, see Specification, Example 3.

Lastly, the Office maintains that it would have been obvious to "employ an analog, homolog, isomer, bioisostere, salt, acid or ester" of a known compound for the same use, and that the prior art (specifically Block et al., (presumably Block II) col. 1, paragraph 1) teaches N-alkyl-DNJ derivatives for treating hepatitis. Contrary to the Office's assertion, however, none of Block I or II, Repp et al. or Gish et al. teach N-alkyl-DNJ derivatives generally. Block I refers only to N-butyl-DNJ, and Block II is limited to N-alkyl groups with three to six carbon atoms. Repp et al. teach only N-methyl-DNJ as an inhibitor of MHV, and Gish et al. make no mention of N-alkyl DNJ compounds. In any event, disclosure of certain N-alkyl-DNJ derivatives outside the scope of claims 37-73 as inhibitors of hepatitis virus does not render obvious the compositions of the instant application, for the reasons given above. The art neither suggests the use of N-substituted-DNJ compounds in combination with nucleosides or nucleotides to treat hepatitis infection, otherwise provides any motivation to make such combination, nor provides any reasonable basis for expecting that the combination would offer any benefit or advantage.

Applicants thus respectfully submit that the Office has failed to establish that claims 37-73 are *prima facie* obvious in view of Block I, Block II, Repp et al., Gish et al., and Applicants' admissions on the record, and further submit that these claims are not obvious in view of these references or the prior art as a whole.

VERSION WITH MARKINGS SHOWING CHANGES MADE

IN THE TITLE:

The Title has been replaced with the following:

PHARMACEUTICAL COMPOSITIONS COMPRISING N-SUBSTITUTED-1,5-DIDEOXY-1,5-IMINO-D-GLUCITOL COMPOUNDS IN COMBINATION THERAPY

IN THE CLAIMS:

Claims 1-34 and 36 have been cancelled.

Claim 37 has been amended as follows:

37. (Once amended) The pharmaceutical composition of claim **[36]** 70, wherein said first and second amounts of said compounds together comprise an anti-hepatitis virus effective amount of said compounds.

Claim 38 has been amended as follows:

38. (Once amended) The pharmaceutical composition of claim **[36]** 70, wherein R is a branched or straight chain alkyl having **[a chain length of C_1 to C_{20}]** **seven or more carbon atoms**, and W, X, Y, and Z are each hydrogen.

Claim 39 has been amended as follows:

39. (Once amended) The pharmaceutical composition of claim 38, wherein R is a straight chain alkyl having a chain length of **[C_1]** C_7 to C_{20}.

Claim 40 has been amended as follows:

40. (Once amended) The pharmaceutical composition of claim 39, wherein R is a straight chain alkyl having a chain length of **[C_2]** C_7 to C_{14}.

Claim 41 has been amended as follows:

41. (Once amended) The pharmaceutical composition of claim 40, wherein R is a straight chain alkyl having a chain length of **[C_6]** **C**$_7$ to C_{12}.

Claim 43 has been amended as follows:

43. (Once amended) The pharmaceutical composition of claim **[36]** **70**, wherein R is a branched or straight chain alkyl having **[a chain length of C_1 to C_{20}]** **seven or more carbon atoms**, and W, X, Y, and Z are each alkanoyl.

Claim 44 has been amended as follows:

44. (Once amended) The pharmaceutical composition of claim 43, wherein R is a straight chain alkyl having a chain length of **[C_1]** **C**$_7$ to C_{20}.

Claim 45 has been amended as follows:

45. (Once amended) The pharmaceutical composition of claim 44, wherein R is a straight chain alkyl having a chain length of **[C_2]** **C**$_7$ to C_{14}.

Claim 46 has been amended as follows:

46. (Once amended) The pharmaceutical composition of claim 45, wherein R is a straight chain alkyl having a chain length of **[C_6]** **C**$_7$ to C_{12}.

Claim 53 has been amended as follows:

53. (Once amended) The pharmaceutical composition of claim **[36]** **70**, wherein

R is a straight chain alkyl having a chain length of **[C_1]** **C**$_7$ to C_{20},

W, X, Y, and Z are each hydrogen, and

said antiviral compound is a nucleoside antiviral compound.

Claim 54 has been am nded as follows:

54. (Once amended) The pharmaceutical composition of claim **[36]** 70, wherein

R is a straight chain alkyl having a chain length of **[C_1]** C_7 to C_{20},

W, X, Y, and Z are each butanoyl, and

said antiviral compound is a nucleoside antiviral compound.

Claim 55 has been amended as follows:

55. (Once amended) The pharmaceutical composition of claim **[36]** 70, wherein said *N*-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound is selected from the group consisting of:

[*N*-(n-hexyl-)-1,5-dideoxy-1,5-imino-D-glucitol;]

N-(n-heptyl-)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(n-octyl-)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(n-octyl-)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(n-nonyl-)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(n-decyl-)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(n-undecyl-)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(n-nonyl-)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(n-decyl-)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(n-undecyl-)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(n-dodecyl-)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(2-ethylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(4-ethylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(5-methylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(3-propylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol;

***N*-(1-pentylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol;**

[*N*-(1-pentylpentylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol;]

N-(1-butylbutyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(7-methyloctyl-)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(8-methylnonyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(9-methyldecyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(10-methylundecyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(6-cyclohexylhexyl-)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(4-cyclohexylbutyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(2-cyclohexylethyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(1-cyclohexylmethyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(1-phenylmethyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(3-phenylpropyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(3-(4-methyl)-phenylpropyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(6-phenylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol;

N-(n-nonyl-)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(n-decyl-)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(n-undecyl-)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(n-dodecyl-)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(2-ethylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(4-ethylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(5-methylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(3-propylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(1-pentylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

[*N*-(1-pentylpentylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;]

N-(1-butylbutyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(7-methyloctyl-)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(8-methylnonyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(9-methyldecyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(10-methylundecyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(6-cyclohexylhexyl-)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(4-cyclohexylbutyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(2-cyclohexylethyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(1-cyclohexylmethyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(1-phenylmethyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(3-phenylpropyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate;

N-(3-(4-methyl)-phenylpropyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate; and

N-(6-phenylhexyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate, and

said nucleoside or nucleotide antiviral compound is selected from the group consisting of:

(+)-cis-5-fluoro-1-[2-(hydroxy-methyl)-[1,3-oxathiolan-5-yl]cytosine;

(-)-2'-deoxy-3'-thiocytidine-5'-triphosphate (3TC);

(-)-cis-5-fluoro-1-[2-(hydroxy-methyl)-[1,3-oxathiolan-5-yl]cytosine (FTC);

(-)2',3', dideoxy-3'-thiacytidine [(-)-SddC];

1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)-5-iodocytosine (FIAC);

1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)-5-iodocytosine triphosphate (FIACTP);

1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)-5-methyluarcil (FMAU);

1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide;

2',3'-dideoxy-3'-fluoro-5-methyl-dexocytidine (FddMeCyt);

2',3'-dideoxy-3'-chloro-5-methyl-dexocytidine (ClddMeCyt);

2',3'-dideoxy-3'-amino-5-methyl-dexocytidine (AddMeCyt);

2',3'-dideoxy-3'-fluoro-5-methyl-cytidine (FddMeCyt);

2',3'-dideoxy-3'-chloro-5-methyl-cytidine (ClddMeCyt);

2',3'-dideoxy-3'-amino-5-methyl-cytidine (AddMeCyt);

2',3'-dideoxy-3'-fluorothymidine (FddThd);

2',3'-dideoxy-beta-L-5-fluorocytidine (beta-L-FddC);

2',3'-dideoxy-beta-L-5-thiacytidine;

2',3'-dideoxy-beta-L-5-cytidine (beta-L-ddC);

2'-deoxy-3'-thia-5-fluorocytosine;

3'-amino-5-methyl-dexocytidine (AddMeCyt);

3'-azido-3'-deoxythymidine (AZT);

3'-chloro-5-methyl-dexocytidine (ClddMeCyt);

9-(2-phosphonyl-methoxyethyl)-2',6'-diaminopurine-2',3'-dideoxyriboside;

9-(2-phosphonylmethoxyethyl)adenine (PMEA);

acyclovir triphosphate (ACVTP);

D-carbocyclic-2'-deoxyguanosine (CdG);

dideoxy-cytidine;

dideoxy-cytosine (ddC);

dideoxy-guanine (ddG);

dideoxy-inosine (ddI);

E-5-(2-bromovinyl)-2'-deoxyuridine triphosphate;

fluoro-arabinofuranosyl-iodouracil;

stavudine;

2-deoxy-3'-thia-5-fluorocytidine;

2',3'-dideoxy-guanine; and

2',3'-dideoxy-guanosine.

Claim 56 has been amend d as follows:

56. (Once amended) The pharmaceutical composition of claim **[36]** 70, wherein said *N*-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound is selected from the group consisting of *N*-(n-nonyl)-1,5-dideoxy-1,5-imino-D-glucitol and *N*-(n-nonyl)-1,5-dideoxy-1,5-imino-D-glucitol, tetrabutyrate, and said nucleoside antiviral compound is (-)-2'-deoxy-3'-thiocytidine-5'-triphosphate (3TC).

Claim 58 has been amended as follows:

58. (Once amended) The pharmaceutical composition of claim **[36]** 70, wherein said first amount of said *N*-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound is in the range of from about 0.1 mg to about 100 mg.

Claim 61 has been amended as follows:

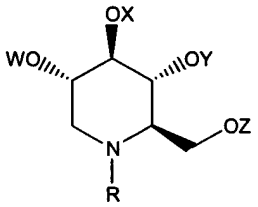
61. (Once amended) The pharmaceutical composition of claim **[36]** 70, wherein said second amount of said nucleoside or nucleotide antiviral compound, or mixture thereof, is in the range of from about 0.1 mg to about 500 mg.

Claim 65 has been amended as follows:

65. (Once amended) The pharmaceutical composition of claim **[36]** 70, wherein said second amount of said nucleoside or nucleotide antiviral compound, or mixture thereof, is in the range of from about 1 mg to about 50 mg.

Claim 66 has been amended as follows:

66. (Once amended) A pharmaceutical composition for treating a hepatitis B virus infection in a mammal, comprising from about 0.1 mg to about 100 mg of an *N*-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I:



I

wherein:

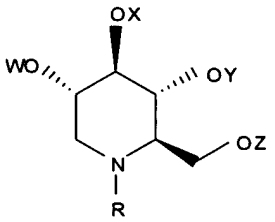
R is selected from the group consisting of arylalkyl, cycloalkylalkyl, and branched or straight chain alkyl having a chain length of **[C_1]** **$\underline{C}_7$** to C_{20}, and

W, X, Y, and Z are each independently selected from the group consisting of hydrogen, alkanoyl, aroyl, and trifluoroalkanoyl; and

from about 0.1 mg to about 500 mg of a compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral, and mixtures thereof.

Claim 70 has been amended as follows:

70. (once amended) A pharmaceutical composition, comprising a first amount of an *N*-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I:



wherein:

R is selected from the group consisting of arylalkyl, cycloalkylalkyl, and branched or straight chain alkyl having **[a chain length greater than C_6]** **<u>seven or more carbon atoms</u>**, and

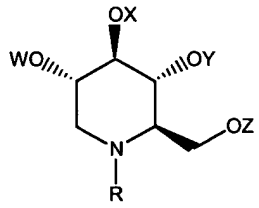
W, X, Y, and Z are each independently selected from the group consisting of hydrogen, alkanoyl, aroyl, and trifluoroalkanoyl; and

a second amount of an antiviral compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and mixtures thereof, and

a pharmaceutically acceptable carrier, diluent, or excipient.

Claim 71 has been amended as follows:

71. (Once amended) A pharmaceutical composition, comprising a first amount of an *N*-substituted-1,5-dideoxy-1,5-imino-D-glucitol compound of Formula I:



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wherein:

R is selected from the group consisting of arylalkyl, cycloalkylalkyl, and branched or straight chain alkyl having a chain length of between **[C_6 and C_{12}]** **C_7 and C_{20}**, and

W, X, Y, and Z are each independently selected from the group consisting of hydrogen, alkanoyl, aroyl, and trifluoroalkanoyl; and

a second amount of an antiviral compound selected from the group consisting of a nucleoside antiviral compound, a nucleotide antiviral compound, and mixtures thereof, and

a pharmaceutically acceptable carrier, diluent, or excipient.

CONCLUSION

In view of the foregoing remarks, it is respectfully submitted that the specification and claims 37-54 and 58-66 conform with the requirements of 35 U.S.C. § 112, first and second paragraphs; that claims 37-40, 43-45 and 48-51 satisfy the requirements of § 102; and that claims 37-73 satisfy the requirements of § 103. Favorable reconsideration and early allowance of all claims are respectfully requested.

The Commissioner is hereby authorized to charge any additional fees required under § 1.17 or refund any overpayment to Deposit Account No. 19-1345.

Respectfully submitted,

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